UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

**Date:** February 1, 2005

**MEMORANDUM**

**Subject:** EPA File Symbol: 352-ALE DUPONT ADVION COCKROACH GEL BAIT
DP Barcode: D312433
Decision No.: 352628
PC Code: 067710 Indoxacarb

**From:** Byron T. Backus, Ph.D.
Technical Review Branch
Registration Division (7505C)

Byron T. Backus
Feb-1-2005
JCH

**To:** Ann Hanger/John Hebert, RM07
Insecticide Branch
Registration Division (7505C)

**Applicant:** E.I. DUPONT DE NEMOURS AND CO., INC

**FORMULATION DECLARATION FROM LABEL:**

| Active Ingredient(s): | % by wt. |
|---|---|
| Indoxacarb (S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4(trifluromethoxy) phenyl] amino]carbonyl]indeno-[1,2-e][1,3,4]oxadiazine-4a-(3H)-carboxylate | 0.6% |
| Other Ingredients: | 99.4% |
| Total: | 100.00% |

**ACTION REQUESTED:**

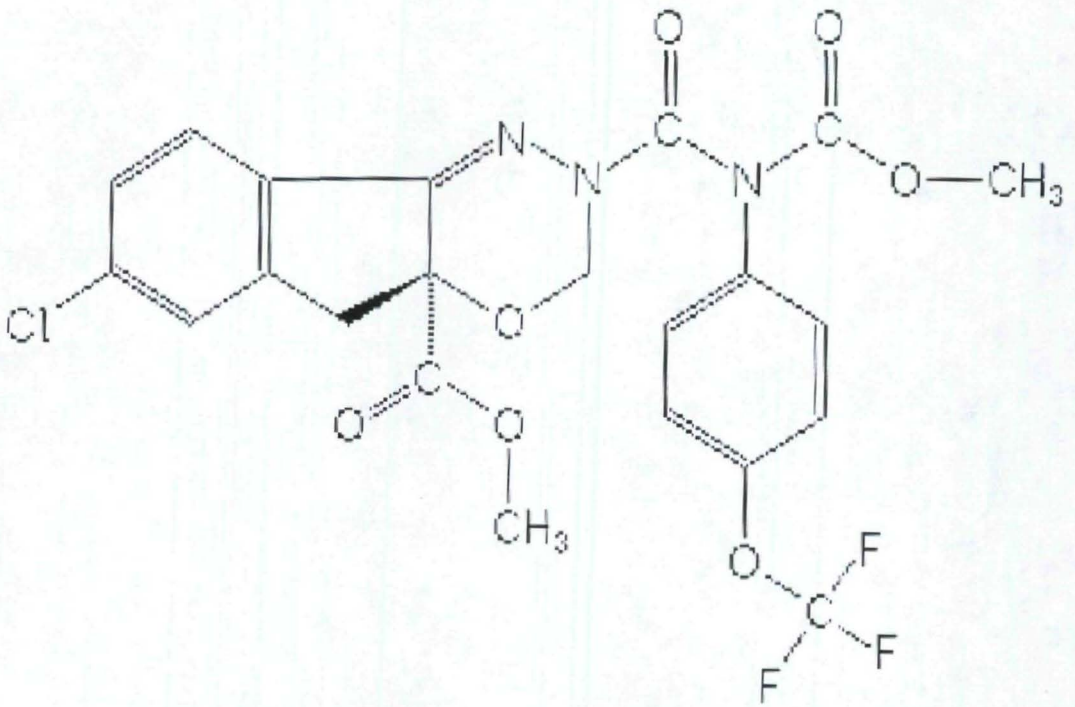
The Product Manager requests:

"Please review the acute toxicity studies submitted to support the registration of

the new end-use indoxacarb product, file symbol 352-ALE. The MRIDs are 464505-03, 464505-04, 464417-05 (inhalation waiver), 464505-05, 464505-06, and 464505-07."

## BACKGROUND:

The following is the structure of Indoxacarb ($C_{22}H_{17}ClF_3N_3O_7$; PC 067710; CAS# 173584-44-6), the active ingredient in this formulation:



This package includes an acute oral $LD_{50}$ study (rat, up-and-down method, defaulting to a limit test at 5000 mg/kg: MRID 46450503); acute dermal $LD_{50}$ study (rat; MRID 46450504); primary eye irritation study (rabbit; MRID 46450505); primary dermal irritation study (rabbit; 46450506) and a Local Lymph Node Assay (LLNA) in mice (MRID 46450507). These five studies were conducted at E.I. du Pont de Nemours and Company Haskell Laboratory for Health and Environmental Sciences, Newark, DE 19714-0050.

These studies were conducted on a formulation identified as DPX-MP062-411, a brown gel bait formulation containing 0.6% DPX-KN128 active ingredient

## RECOMMENDATIONS:

1. The five acute toxicity studies have been reviewed and classified as acceptable.

2. Based on the physical form (a gel) of this product, the low percentage (0.6%) of active ingredient, and the low (toxicity category IV) inhalation toxicity of the manufacturing use product (52.7% active) TRB concludes that a waiver of the inhalation study requirement for 352-ALE is appropriate and that this formulation can be assigned to EPA Toxicity Category IV in terms of its inhalation exposure hazard potential.

3. Based on the results of the acute toxicity studies, the following is the acute toxicity profile for EPA File Symbol: 352-ALE DUPONT ADVION COCKROACH GEL BAIT:

| Study Type | Tox. Cat. | Classification & MRID # |
|---|---|---|
| Acute Oral $LD_{50}$ (rat) | IV | Acceptable (#46450503) |
| Acute Dermal $LD_{50}$ (rat) | IV | Acceptable (#46450504) |
| Acute Inhalation $LC_{50}$ (rat) | IV | Waived |
| Primary Eye Irritation (rabbit) | IV | Acceptable (#46450505) |
| Primary Dermal Irritation (rabbit) | IV | Acceptable (#46450506) |
| Sensitization (LLNA-mouse) | Negative | Acceptable (#46450507) |

4. The appropriate signal word is CAUTION, as proposed by the registrant.

5. Based on the acute toxicity profile and proposed uses, the following is the precautionary labeling for this product, as obtained from the Label Review System.

**PRODUCT ID #:** **000352-00652**

**PRODUCT NAME:** **DUPONT ADVION COCKROACH GEL BAIT**

**PRECAUTIONARY STATEMENTS**

**SIGNAL WORD:** **CAUTION**

***Hazards to Humans and Domestic Animals:***

[None required: registrant has proposed the following which is acceptable: Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling; in addition there is a label statement: AVOID TREATING AREAS THAT ARE EASILY ACCESSIBLE TO CHILDREN AND PETS].

**First Aid:**

[None required: registrant has proposed the following which is acceptable: Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact 1-800-441-3637 for emergency medical treatment information].

**Reviewer:** Byron T. Backus, Ph.D. **Date:** January 31, 2005
**Risk Manager (EPA):** 07

**STUDY TYPE:** Acute Oral Toxicity - Up-and-Down Method; albino Rat; OPPTS 870.1100; OECD 425

**TEST MATERIAL (% a.i.):** DPX-MP062-411, a formulation (gel bait) containing 0.6% DPX-KN128 active ingredient (Indoxacarb; ($C_{22}H_{17}ClF_3N_3O_7$; PC 067710; CAS# 173584-44-6); (S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4(trifluromethoxy) phenyl] amino]carbonyl]indeno-[1,2-*e*][1,3,4]oxadiazine-4a-(3*H*)-carboxylate). Described as a brown gel.

**SYNONYMS:** Du Pont Advion Cockroach Gel Bait

**CITATION:** Finlay, C. (2004) Indoxacarb (DPX-MP062) 0.6RB: Acute Oral Toxicity Study in Rodents - Up-and-Down Procedure. Laboratory Project ID: DuPont-15596. Study Completion Date: Nov. 30, 2004. Unpublished study prepared by E. I. Du Pont de Nemours and Company Haskell[SM] Laboratory for Health and Environmental Sciences, Newark, DE 19714-0050. 27p. MRID 46450503.

**SPONSOR:** E. I. Du Pont De Nemours and Co., Inc.

**EXECUTIVE SUMMARY:** In an acute oral (Up-and-Down Method, defaulting to Limit Test) toxicity study (MRID 46450503), a total of 3F fasted (17-17.5 hrs) Crl:CD®(SD)IGS BR female rats (source: Charles River Laboratories, Inc., Raleigh, NC; age: about 10 weeks old; weights (fasted) 199.3 to 209.5 g) were orally gavaged with 5000 mg DPX-MP062-411 (a brown gel containing 0.6% DPX-KN128, the active ingredient) per kg body weight. For purposes of dosage the test material was suspended in deionized water; this suspension was administered at 10 mL per kg of body weight.

On the day of dosage rats were observed four times after dosage for clinical signs of toxicity and mortality and then once daily for the remainder of the 14-day observation period. Individual body weights were recorded after fasting and just prior to dosing (Day 0) and on days 7 and 14.

All rats survived and there were no signs of toxicity. All 3 rats gained weight in the period from day 0 to day 7 and again from day 7 to 14. At post-sacrifice necropsy there were no observed abnormalities.

Observed Oral $LD_{50}$ Females > 5000 mg/kg (0/3 died following dosage at this level)

DPX-MP062-411 (containing 0.6% DPX-KN128, the active ingredient), a brown gel, is in EPA Toxicity Category IV for oral toxicity based on the observed $LD_{50}$ (>5000 mg/kg) in female rats.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

**COMPLIANCE:** Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

**RESULTS and DISCUSSION:**

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Monday, January 31, 2005, 2:17:50 PM
Data file name: Indoxacarb(DPX-MP062).dat
Last modified: 1/31/2005 2:17:46 PM

Test/Substance: Enter test description.
Test type: Limit Test
Limit dose (mg/kg): 5000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

DATA:

| Test Seq. | Animal ID | Dose (mg/kg) | Short-term Result | Long-term Result |
|---|---|---|---|---|
| 1 | 7049 | 5000 | O | O |
| 2 | 8408 | 5000 | O | O |
| 3 | 8409 | 5000 | O | O |

(X = Died, O = Survived)

Dose Recommendation: The limit test is complete.

SUMMARY OF LONG-TERM RESULTS:

| Dose | O | X | Total |
|---|---|---|---|
| 5000 | 3 | 0 | 3 |
| All Doses | 3 | 0 | 3 |

Statistical Estimates:

The LD50 is greater than 5000 mg/kg.

| Dose (mg/kg bw) | Mortality/Number Tested | | |
|---|---|---|---|
| | Males | Females | Combined |
| 5000 | - | 0/3 | 0/3 |

**Statistics** - Not necessary to compute the oral $LD_{50}$.

**A. Mortality** - None.

**B. Clinical observations** - No symptoms. All 3 rats gained weight in the period from day 0 to day 7 and again from day 7 to 14.

**C. Gross Necropsy** - At necropsy, there were no observed abnormalities.

**D. Reviewer's Conclusions:** The study is acceptable. Based on the rat female $LD_{50} > 5000$ DPX-MP062-411 (a brown gel containing 0.6% DPX-KN128, the active ingredient) is in EPA Toxicity Category IV in terms of oral toxicity.

**E. Deficiencies** - None

**Reviewer:** Byron T. Backus, Ph.D. **Date:** January 31, 2005
**Risk Manager (EPA):** 07

**STUDY TYPE:** Acute Dermal Toxicity - albino rat - OPPTS 870.1200; OECD 402

**TEST MATERIAL (% a.i.):** DPX-MP062-411, a formulation (gel bait) containing 0.6% DPX-KN128 active ingredient (Indoxacarb;($C_{22}H_{17}ClF_3N_3O_7$; PC 067710; CAS# 173584-44-6); (S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4(trifluromethoxy) phenyl] amino]carbonyl]indeno-[1,2-*e*][1,3,4]oxadiazine-4a-(3*H*)-carboxylate). Described as a brown paste.

**SYNONYMS:** Du Pont Advion Cockroach Gel Bait

**CITATION:** Finlay, C. (2004) Indoxacarb (DPX-MP062) 0.6RB: Acute Dermal Toxicity Study in Rats. Laboratory Project ID: DuPont-15603. Study Completion Date: Nov. 30, 2004. Unpublished study prepared by E. I. Du Pont de Nemours and Company Haskell[SM] Laboratory for Health and Environmental Sciences, Newark, DE 19714-0050. 35p. MRID 46450504.

**SPONSOR:** E. I. Du Pont De Nemours and Co., Inc.

**EXECUTIVE SUMMARY:** In an acute dermal toxicity study (MRID 46450504), a group (5M & 5F) of Crl:CD®(SD)IGS BR rats (source: Charles River Laboratories, Inc., Raleigh, NC; age: males: about 9 weeks old; females: about 10 weeks old; weights: males: 281.9 to 316.6 g; females: 214.6-249.3 ) were dermally exposed for 24 hours to 5000 mg DPX-MP062-411 (a brown paste containing 0.6% DPX-KN128, the active ingredient) per kg body weight. The test material covered approximately 37 $cm^2$ on each rat; the test material was covered with a 2-ply gauze patch, and rats were wrapped with a stretch gauze bandage and self-adhesive bandage. Collars were placed on the rats to prevent them from removing the wrappings or ingesting the test substance.

The collars, wrappings and remaining test material was removed after 24 hours. At that time and subsequently on a daily basis the rats were observed for signs of toxicity and dermal effects; the latter were scored according to Draize. Survivors were sacrificed on day 15 and their bodies were grossly necropsied.

There was no mortality. Some of the rats showed black discharge from both eyes on day 1 (possibly due to the collaring, as they may have been unable to groom themselves); otherwise there was no sign of systemic toxicity. All rats had grade 1 or 2 erythema on day 1 and one had grade 1 edema; 3 rats still had erythema on day 2 but this had cleared by day 5. One rat had a dorsal scab on days 5 through 7. All rats had weight gains from day 0 to 7 and again from day 7 to 14.

No gross abnormalities were observed at post-sacrifice necropsy.

Dermal $LD_{50}$ Males > 5000 mg/kg (0/5 died)
Females > 5000 mg/kg (0/5 died)
Combined > 5000 mg/kg (0/10 died)

Based on the $LD_{50}$ > 5000 mg/kg, DPX-MP062-411 (containing 0.6% DPX-KN128, the active ingredient), a brown paste, is in EPA Toxicity Category IV for dermal toxicity.

This acute dermal study is classified as acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

**COMPLIANCE:** Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

**RESULTS and DISCUSSION:**

| Dose (mg/kg bw) | Mortality/Number Tested | | |
|---|---|---|---|
| | Males | Females | Combined |
| 5000 | 0/5 | 0/5 | 0/10 |

**Statistics** - Not necessary to compute the dermal $LD_{50}$.

**A. Mortality** - None, as noted in the table above.

**B. Clinical observations** - Some of the rats showed black discharge from both eyes on day 1 (possibly due to the collaring, as they may have been unable to groom themselves); otherwise there was no sign of systemic toxicity. All rats had grade 1 or 2 erythema on day 1 and one had grade 1 edema; 3 rats still had erythema on day 2 but this had cleared by day 5. One rat had a dorsal scab on days 5 through 7. All rats had weight gains from day 0 to 7 and again from day 7 to 14.

**C. Gross Necropsy** - No gross abnormalities were observed at post-sacrifice necropsy.

**D. Reviewer's Conclusions:** The study is acceptable. Based on the $LD_{50}$ > 5000 mg/kg, DPX-MP062-411 (containing 0.6% DPX-KN128, the active ingredient), a brown paste is in EPA Toxicity Category IV in terms of dermal toxicity.

**E. Deficiencies** - None

**Reviewer:** Byron T. Backus, Ph.D. **Date:** January 31, 2005
**Risk Manager (EPA):** 07

**STUDY TYPE:** Primary Eye Irritation - NZW Rabbit; OPPTS 870.2400; OECD 405

**TEST MATERIAL (% a.i.):** DPX-MP062-411, a formulation (gel bait) containing 0.6% DPX-KN128 active ingredient (Indoxacarb; ($C_{22}H_{17}ClF_3N_3O_7$; PC 067710; CAS# 173584-44-6); (S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4(trifluromethoxy) phenyl] amino]carbonyl]indeno-[1,2-*e*][1,3,4]oxadiazine-4a-(3*H*)-carboxylate). Described as a brown gel with a pH of 6.3.

**SYNONYMS:** Du Pont Advion Cockroach Gel Bait

**CITATION:** Finlay, C. (2004) Indoxacarb (DPX-MP062) 0.6RB: Acute Eye Irritation Study in Rabbits. Laboratory Project ID: DuPont-15599. Study Completion Date: Nov. 29, 2004. Unpublished study prepared by E. I. Du Pont de Nemours and Company Haskell[SM] Laboratory for Health and Environmental Sciences, Newark, DE 19714-0050. 23p. MRID 46450505.

**SPONSOR:** E. I. Du Pont De Nemours and Co., Inc.

**EXECUTIVE SUMMARY:** In a primary eye irritation study (MRID 46450505), 0.1 mL of DPX-MP062-411, a formulation (gel bait) containing 0.6% DPX-KN128 active ingredient (Indoxacarb) was instilled into the conjunctival sac of one eye of each of 3 young adult male New Zealand White rabbits (source: Covance Research Products, Denver, Pennsylvania). Eyes were scored (Draize) at 1, 24, 48 and 72 hours after instillation.

Two of the rabbits pawed their treated eyes after instillation. Two eyes scored zero for all irritation effects at 1 hour; the remaining eye scored "1" for redness and "1" for discharge. All eyes scored zero for (were completely clear of) all irritation effects at 24, 48 and 72 hours.

In this study, DPX-MP062-411, a formulation (gel bait) containing 0.6% DPX-KN128 active ingredient (Indoxacarb), is in EPA Toxicity Category IV for eye exposure based on the lack of eye irritation (all scores zero) at 24 hours.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

**COMPLIANCE:** Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

**RESULTS AND DISCUSSION:**

| Observations | Number "positive"/number tested | | | |
|---|---|---|---|---|
| | 1 hr | 24 hr | 48 hr | 72 hr |
| Corneal Opacity | 0/3 | 0/3 | 0/3 | 0/3 |
| Iritis | 0/3 | 0/3 | 0/3 | 0/3 |
| Conjunctivae: | | | | |
| Redness[1] | 0/3 | 0/3 | 0/3 | 0/3 |
| Chemosis[1] | 0/3 | 0/3 | 0/3 | 0/3 |
| Discharge[1] | 0/3 | 0/3 | 0/3 | 0/3 |

[1]Score of 2 or more considered positive

**A. Observations** - Two of the rabbits pawed their treated eyes after instillation. Two eyes scored zero for all irritation effects at 1 hour; the remaining eye scored "1" for redness and "1" for discharge. All eyes scored zero for (were completely clear of) all irritation effects at 24, 48 and 72 hours.

**B. Reviewer's Conclusions:** The study adequately defines an EPA Toxicity Category IV eye exposure hazard potential for DPX-MP062-411, a formulation (gel bait) containing 0.6% DPX-KN128 active ingredient (Indoxacarb), based on the lack of eye irritation (all scores zero) at 24 hours.

**C. Deficiencies** - None

**Reviewer:** Byron T. Backus, Ph.D. **Date:** January 31, 2005
**Risk Manager (EPA):** 07

**STUDY TYPE:** Primary Dermal Irritation - NZW Rabbit; OPPTS 870.2500; OECD 404
Primary Eye Irritation - NZW Rabbit; OPPTS 870.2400; OECD 405

**TEST MATERIAL (% a.i.):** DPX-MP062-411, a formulation (gel bait) containing 0.6% DPX-KN128 active ingredient (Indoxacarb; ($C_{22}H_{17}ClF_3N_3O_7$; PC 067710; CAS# 173584-44-6); (S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4(trifluromethoxy) phenyl] amino]carbonyl]indeno-[1,2-*e*][1,3,4]oxadiazine-4a-(3*H*)-carboxylate). Described as a brown gel with a pH of 6.3.

**SYNONYMS:** Du Pont Advion Cockroach Gel Bait

**CITATION:** Finlay, C. (2004) Indoxacarb (DPX-MP062) 0.6RB: Acute Dermal Irritation Study in Rabbits. Laboratory Project ID: DuPont-15598. Study Completion Date: Nov. 8, 2004. Unpublished study prepared by E. I. Du Pont de Nemours and Company Haskell[SM] Laboratory for Health and Environmental Sciences, Newark, DE 19714-0050. 23p. MRID 46450506.

**SPONSOR:** E. I. Du Pont De Nemours and Co., Inc.

**EXECUTIVE SUMMARY:** In a primary dermal irritation study (MRID 46450506), doses of 0.5 mL DPX-MP062-411, a formulation (a brown gel with a pH of 6.3) containing 0.6% DPX-KN128 active ingredient (Indoxacarb) were applied to single dermal sites on each of 3 male New Zealand White young adult rabbits (source: Covance Research Products, Denver, Pennsylvania), with 4-hour semi-occluded exposure. After 4 hours the semi-occlusive dressing and remaining test material were removed. Test sites were scored (Draize) at approximately 1, 24, 48 and 72 hrs.

All sites consistently scored zero for both erythema and edema. The PII = 0.00.

In this study DPX-MP062-411, a brown gel with a pH of 6.3 containing 0.6% DPX-KN128 (Indoxacarb) active ingredient is in EPA Toxicity Category IV for dermal irritation effects, based on the lack of any irritation effects (all scores zero at 1, 24, 48 and 72 hours; PII = 0.00) following 4-hour semi-occluded exposure.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

**COMPLIANCE:** Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

**RESULTS and DISCUSSION:**

**A. Observations** - All sites consistently scored zero for both erythema and edema.

**B. Results** - The PII (average of 1, 24, 48 and 72-hour scores) = 0.00.

**C. Reviewer's Conclusions** - The study adequately demonstrates a Toxicity Category IV hazard potential in terms of dermal irritation for DPX-MP062-411, a brown gel with a pH of 6.3 containing 0.6% DPX-KN128 (Indoxacarb) active ingredient.

**D. Deficiencies** - None

**Reviewer:** Byron T. Backus, Ph.D. **Date:** February 1, 2005
**Product Manager (EPA):** 07

**STUDY TYPE:** Dermal Sensitization - female CBA/JHsd mice; OPPTS 870.2600; OECD 406, 429

**TEST MATERIAL (% a.i.):** DPX-MP062-411, a formulation (gel bait) containing 0.6% DPX-KN128 as active ingredient (Indoxacarb; ($C_{22}H_{17}ClF_3N_3O_7$; PC 067710; CAS# 173584-44-6); (S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4(trifluromethoxy) phenyl] amino]carbonyl]indeno-[1,2-*e*][1,3,4]oxadiazine-4a-(3*H*)-carboxylate; CAS #173584-44-6). Described as a brown gel with a pH of 6.3.

**SYNONYMS:** Du Pont Advion Cockroach Gel Bait

**CITATION:** Ladics, G.S. (2004) Indoxacarb (DPX-MP062) 0.6RB: Local Lymph Node Assay (LLNA) in Mice. Laboratory Project ID: DuPont-15601. Study Completion Date: Oct. 22, 2004. Unpublished study prepared by E. I. Du Pont de Nemours and Company Haskell[SM] Laboratory for Health and Environmental Sciences, Newark, DE 19714-0050. 46p. MRID 46450507.

**SPONSOR:** E. I. Du Pont De Nemours and Co., Inc.

**EXECUTIVE SUMMARY:** In a dermal sensitization study (MRID 46450507) with DPX-MP062-411, a brown gel containing 0.6% DPX-KN128 (Indoxacarb) as active ingredient and DMSO as solvent, groups, each consisting of 5 female CBA/JHsd mice (age at testing: about 8 weeks; body weights: 17.6-24.1 g; source: Harlan Sprague Dawley, Frederick, MD) were tested using the Local Lymph Node Assay (LLNA) protocol. DMSO was used to dilute the test material (tested at 1, 5, 25 and 100% dilutions). The positive control was alpha-hexylcinnamaldehyde (solvent: 4:1 acetone:olive oil). 25 µl applications of the test material and/or positive control material and their respective vehicle controls were made on days 0, 1 and 2. There were no systemic clinical signs or local dermal effects associated with exposure to DPX-KN128, and no significant findings at post-sacrifice necropsy.

On day 5 each mouse was intravenously injected with 20 µCi of $^3$H-Thymidine. About 5 hours after this injection mice were sacrificed, draining auricular lymph nodes were removed and single cell suspensions prepared, which were incubated overnight. On day 6 the single cell suspensions were counted on a beta counter. A stimulation index (SI) was obtained by calculating the mean activity (dpm) of each experimental group by the dpm of their respective vehicle control group. There were no indications of a dermal sensitization effect (SI > 3.0) associated with exposure to 0.6% DPX-KN128. The positive control material (25% alpha hexylcinnamaldehyde in 4:1 acetone:olive oil) gave an appropriate response (SI = 8.8).

In this study, **DPX-MP062-411, a brown gel containing 0.6% DPX-KN128 (Indoxacarb) is not a dermal sensitizer.**

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2600; OECD 406, 429) in the Guinea pig .

**COMPLIANCE:** Signed and dated GLP (p. 3), Quality Assurance (p. 4), and [No] Data Confidentiality (p. 2) statements were provided.

## I. MATERIALS and METHODS

| | | |
|---|---|---|
| 1. | **Radio Isotope** | $^{3}$H-Thymidine |
| | **Description:** | (not stated) |
| | **Lot/Batch #:** | (not stated) |
| | **Radio-Purity:** | (not stated) |
| | **CAS #:** | (not stated) |
| | **Date of Isotope Activity Assay:** | (not stated) |
| | **Date of use in bio-Assay:** | (not stated) |

**2. Vehicle and/or positive control** - Dimethyl sulfoxide (used as vehicle control and diluting material for Indoxacarb (DPX-MP062) 0.6RB; 25% hexylcinnamaldehyde in 4:1 acetone/olive oil was used as positive control. In addition, the positive control vehicle was also tested.

**3. Animal assignment and treatment** - Five groups of 5 female CBA/JHsd mice were dosed with 0% (vehicle control), 1%, 5%, 25% or 100% Indoxacarb 0.6RB on both ears. Dimethylsulfoxide was used as the diluting vehicle. The positive control group consisted of 5 female CBA/JHsd mice dosed with 25% hexylcinnamaldehyde in 4:1 acetone/olive oil. An additional group of 5 mice were dosed with just 4:1 acetone/olive oil.

**4. Dose selection rationale** - "Because Indoxacarb 0.6RB was dosed as a liquid and did not appear to have severe skin-irritating capability (pH ~6.3), the 100% concentration, prepared at 1 g/mL in dimethylsulfoxide (DMSO), was chosen as the high dose."

**5. Treatment preparation and administration** - "25 µl of Indoxacarb 0.6RB were administered topically to the dorsum of each mouse ear for 3 consecutive days (test days 0-2) at dosages listed in the study design [7 groups tested: 0% (DMSO, vehicle control for test substance; 1%, 5%, 25%, 100%; 25% positive control in 4:1 acetone/olive oil, 4:1 acetone/olive oil].

On day 5 an injection containing 20 µCi of $^{3}$H-methyl thymidine ($^{3}$H-TdR) was made into the tail vein of each experimental mouse. Five hours later, the draining Auricular lymph node of each ear was excised into PBS. A single cell suspension of lymph node cells was prepared from each mouse. The single cell suspensions were incubated at 2-8°C overnight. On test day 6, the single cell suspensions were counted on a beta counter. The counts per minute (cpm) data were converted to disintegrations per minute (dpm).

**6. Statistics** - "A stimulation index (SI) was derived for each experimental group by dividing the mean dpm of each experimental group by the mean dpm of the vehicle control group. Statistically significant increases in cell proliferation in the test concentration groups compared to the vehicle control group and/or Sis of greater than or equal to 3.0 indicated a positive response."

"Significance was judged at $p<0.05$ except for dpm data that were judged at $p<0.01$. Lymph node dpm data were transformed to Log to obtain normality or homogeneous variances."

For lymph node data there were preliminary tests for lack of trend, as well as Levene's test for homogeneity and the Shapiro-Wilk test for normality. If the preliminary test was not significant, then there was sequential application of the Jonckheere-Terpstra trend test or one-way analysis of variance followed with Dunnett's test. If the preliminary test was significant, this was followed by the Kruskal-Wallis test followed by Dunn's test.

## II. RESULTS and DISCUSSION:

### A. Disintegrations per Minute/Mouse (group means) -

| Sample Description Test or Control Group | Animal # | Individual Animal DPM [a] | Group Mean DPM ± (SD) | Stimulation Index (SI)* |
|---|---|---|---|---|
| Vehicle Control (DMSO) | 201 | 340.25 | 354.05 ± 140.40 | 1.00[a] |
| | 202 | 523.25 | | |
| | 203 | 403.25 | | |
| | 204 | 136.25 | | |
| | 205 | 367.25 | | |
| 1% Indoxacarb 0.6RB | 401 | 607.25 | 490.85 ± 136.30 | 1.39[a] |
| | 402 | 266.25 | | |
| | 403 | 531.25 | | |
| | 404 | 581.25 | | |
| | 405 | 468.25 | | |
| 5% Indoxacarb 0.6RB | 601 | 473.25 | 692.05 ± 312.61 | 1.95[a] |
| | 602 | 662.25 | | |
| | 603 | 1227.25 | | |
| | 604 | 463.25 | | |
| | 605 | 634.25 | | |
| 25% Indoxacarb 0.6RB | 801 | 474.25 | 429.65 ± 194.51 | 1.21[a] |
| | 802 | 406.25 | | |
| | 803 | 401.25 | | |
| | 804 | 161.25 | | |
| | 2002 | 705.25 | | |
| 100% Indoxacarb 0.6RB | 1001 | 386.25 | 312.65 ± 123.97 | 0.88[a] |
| | 1002 | 203.25 | | |
| | 1003 | 391.25 | | |
| | 1004 | 155.25 | | |
| | 1005 | 427.25 | | |
| 25% Positive control | 1201 | 4117.25 | 3913.00 ± 1694.87 | 8.80[b] |
| | 1202 | 6233.25 | | |
| | 1203 | died | | |
| | 1204 | 2596.25 | | |
| | 1205 | 2705.25 | | |
| Positive control vehicle 4:1 acetone/olive oil | 1401 | 293.25 | 444.65 ± 117.06 | 1.00[b] |
| | 1402 | 362.25 | | |
| | 1403 | 491.25 | | |
| | 1404 | 590.25 | | |
| | 1405 | 486.25 | | |

*** SI = Group mean DPM ÷ Vehicle control mean DPM**
**[a] Compared to results from test article vehicle (DMSO)**
**[b] Compared to results with positive control vehicle (4:1 acetone/olive oil)**

## B. Stimulation Index -

| Sample Description Test or Control Group | Test Material Vehicle | 1% 0.6RB | 5% 0.6RB | 25% 0.6RB | 100% 0.6RB | Positive Control | Positive Control Vehicle |
|---|---|---|---|---|---|---|---|
| Stimulation Index (SI) | 1.00 | 1.39 | 1.95 | 1.21 | 0.88 | 8.80 | 1.00 |
| EC3[b] | n/a | n/a | n/a | n/a | n/a | n/c | n/a |

*b) EC3 is the minimum concentration required to elicit a sensitization reaction (interpolated)*

SI = Group Mean DPM ÷ Vehicle control mean DPM
EC3 = C + [ (3-D) / (B-D) ] * (A-C)
Where (C,D) fall below SI of 3 (C = concentration, D = SI)
(A,B) fall above SI of 3 (A = concentration, B = SI)

**C. Reviewer's Conclusions** - Under the conditions of this assay there was no indication of a sensitization effect (as indicated by an increase in Stimulation Index or SI) associated with exposure to Indoxacarb 0.6RB.

**D. Deficiencies** - None

## ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D312433
2. **PC CODE:** 067710 Indoxacarb (CAS#173584-44-6)
3. **CURRENT DATE:** February 1, 2005
4. **TEST MATERIAL:** DPX-MP062-411, a formulation (gel bait) containing 0.6% DPX-KN128 as active ingredient (Indoxacarb; ($C_{22}H_{17}ClF_3N_3O_7$; PC 067710; CAS# 173584-44-6); (S)-methyl 7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4(trifluromethoxy) phenyl] amino]carbonyl]indeno-[1,2-*e*][1,3,4]oxadiazine-4a-(3*H*)-carboxylate; CAS #173584-44-6). Described as a brown gel with a pH of 6.3, consistent with the proposed product Du Pont Advion Cockroach Gel Bait (EPA File Symbol 352-ALE)

| Study/Species/Lab Study #/Date | MRID | Results | Tox. Cat. | Core Grade |
|---|---|---|---|---|
| Acute oral toxicity/rat/Haskell Laboratory for Health & Environmental Sciences/DuPont-15596/Nov-30-2004 | 46450503 | 3 Sprague-Dawley derived female rats were dosed at 5000 mg/kg. All survived with no signs of toxicity; all gained weight from day 0 to 7 and again from day 7 to 14. No observed abnormalities at post-sacrifice necropsy. | IV | A |
| Acute dermal toxicity/rat/Haskell Laboratory for Health & Environmental Sciences/DuPont-15603/Nov-30-2004 | 46450504 | $LD_{50}$ > 5000 mg/kg. 5M & 5F Sprague-Dawley-derived albino rats were dermally exposed to 5000 mg/kg for 24 hrs; no mortality. No clinical signs; some minor dermal irritation. All gained weight day 0-7 and again day 7-14. No observed abnormalities at post-sacrifice necropsy. | IV | A |
| Primary eye irritation/rabbit/ Haskell Laboratory for Health & Environmental Sciences/DuPont-15599/Nov-29-2004 | 46450505 | Two eyes scored zero for all irritation effects at 1 hr; the third scored 1 (not considered positive) for redness and 1 (not considered positive) for discharge at 1 hr. All eyes scored zero for all irritation at 24, 48 & 72 hrs. | IV | A |
| Primary dermal irritation/rabbit/ Haskell Laboratory for Health & Environmental Sciences/DuPont-15598/Nov-8-2004 | 46450506 | 3 rabbits used; PII = 0.00 with all sites consistently scoring zero for erythema and edema. | IV | A |
| Dermal sensitization - LLNA protocol/female mouse/Haskell Laboratory for Health & Environmental Sciences/DuPont-15601/Oct-22-2004 | 46450507 | Local lymph node assay (LLNA). DMSO was used to dilute test material (to 1%, 5%, 25%, 100% dilutions). Positive control was alpha-hexylcinnamaldehyde in 4:1 acetone:olive oil. No indication of a sensitization reaction. | Not a sensitizer | A |

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**